REMARKS/ARGUMENTS

The foregoing amendments of the claims are of formal nature and do not add new matter. Applicants believe that the current amendments place all claims in *prima facie* condition for allowance or, at least, in a better form for consideration on appeal. Accordingly, the consideration and entry of the present amendment after final rejection is respectfully requested.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional, or continuation-in-part applications.

Claims 28-32 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph.

The remaining rejections of Claims 28-32 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, are addressed below.

I. Information Disclosure Statement

Applicants respectfully thank the Examiner for considering the supplemental information disclosure statement filed on January 10, 2005.

II. Claim Rejections – 35 U.S.C. §101

Claims 28 and 31 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is directed to non-statutory subject matter." In particular, the Examiner asserts that "[t]he claims read on a product of nature in that the claimed antibody is not 'isolated'." (Pages 2-3 of the instant Office Action).

As discussed in the previous Response to Office Action filed January 10, 2005, Applicants, without acquiescing to the Examiner's position in the current rejections, and without prejudice to further prosecution of the subject-matter in one or more continuation or divisional applications, have amended Claim 28 (and, as a consequence, those claims dependent from the same) to recite an "isolated antibody." As discussed in the Response to Office Action filed January 10, 2005, support for this amendment is found in the specification at, for example, page 311, lines 30-39.

This amendment was inadvertently omitted from the Response to Office Action filed January 10, 2005. Applicants thank the Examiner for drawing attention to this issue, and have made the amendment herein.

Thus, the claimed antibodies are distinguished over antibodies in nature and the amendment to Claim 28 (and, as a consequence, those claims dependent from the same) is supported by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection.

III. Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph (Enablement)

Claims 28-32 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (Page 3 of the instant Office Action). In particular, regarding the adipocyte glucose/FFA uptake assay (Example 149), the Examiner alleges that "the data do not support the implicit conclusion of the specification that PRO1760 would be useful for the therapeutic treatment of disorders where the inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes, or hyper- or hypo-insulinemia." The Examiner asserts that "[t]he proposed use of the claimed antibodies that bind PRO1760 polypeptides are simply starting points for further research and investigation into potential practical uses of the polypeptides." (Page 5 of the instant Office Action).

Claims 28-32 also remain rejected under 35 U.S.C. §112, first paragraph, allegedly because "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility one skilled in the art clearly would not know how to use the invention." (Page 7 of the instant Office Action).

Applicants respectfully disagree and traverse the rejections.

Applicants submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1760 polypeptide and for antibodies that specifically bind to the PRO1760 polypeptide.

Utility – Legal Standard

According to 35 U.S.C. § 101:

Whoever invents or discovers any new and *useful* process, machine, manufacture, or

composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1], the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.,* a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4], the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka*[6], the C.A.F.C. reaffirmed *Nelson* and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The Court perceived "no insurmountable

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[1] *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility

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[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (CCPA 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Utility – Application of Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO1760 polypeptide and the claimed antibodies that specifically bind to the PRO1760 polypeptide for the reasons previously set forth in the Applicants' response filed on January 10, 2005, and below.

The Examiner alleges that "Applicant asserts the PRO1760 polypeptide inhibits glucose uptake in adipocyte cells. If one skilled in the art were to administer the PRO1760 polypeptide of the instant application to a patient with obesity, diabetes, and hyper- or hypo-insulinemia, the PRO1760 polypeptide would exacerbate the condition." The Examiner concludes that "the data do not support the implicit conclusion of the specification that PRO1760 would be useful for the

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

therapeutic treatment of disorders where the inhibition of glucose uptake by adipocytes would be beneficial including, for example, obesity, diabetes or hyper-or hypo-insulinemia." (Page 5 of the instant Office Action).

The Examiner states that "one skilled in the art would want to enhance glucose uptake into adipocyte cells" in order to treat disorders such as diabetes. Applicants respectfully point out that the fact that PRO1760 inhibits glucose uptake does not make it useless in such treatment. One of skill in the art would readily understand that a protein which inhibits glucose uptake into adipocytes is a potential therapeutic target, since blocking the function of this protein would decrease the inhibition, and thus increase glucose uptake into adipocytes. One of skill in the art would further understand that antagonists to the PRO1760 polypeptide include antibodies, such as the claimed antibodies which specifically bind the PRO1760 polypeptide. (See the specification at, for example, page 310, lines 2-4). Accordingly, the claimed antibodies are useful in the therapeutic treatment of disorders wherein stimulation of glucose uptake by adipocytes is expected to be therapeutically effective, such as obesity, diabetes, and hyper- or hypo-insulinemia.

Applicants also point out that Mueller *et al.* (1998) disclose that inhibitors of adipocyte glucose uptake, including 2-DG, phloretin, and cytocholasin B, inhibit leptin gene expression and leptin secretion from adipocytes. It was known in the art at the time of filing that leptin is involved in the regulation of food intake, energy expenditure, and body fat stores, and that leptin decreases after fasting or caloric restriction and increases a number of hours after refeeding. (Mueller *et al.* (1998), p. 551, col. 1). One of skill in the art would therefore have understood that agents capable of modulating leptin regulation would be useful in investigations regarding the treatment of obesity. Similarly, PRO1760, as an inhibitor of adipocyte glucose uptake, would be useful as a pharmacological tool for investigation of leptin regulation, in the same way as agents already known and used in the art such as 2-DG, phloretin, and cytocholasin B.

The Examiner further asserts that the various references submitted by Applicants allegedly teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification. The Examiner further asserts that none of the references utilize the stimulatory and inhibitory scale disclosed in the specification. The Examiner asserts that the instant specification "does not report any specific cell numbers or

statistical differences and there is no indication in the specification as to statistically how much the PRO1760 inhibited glucose uptake as compared to control."

Applicants respectfully point out that the Examiner has not provided any evidence that the minor variations in assay protocols disclosed by the various references would be expected to alter the assay results. In fact, the main features of the protocol described in the specification are well within the parameters established in the literature. For example, all the cited references utilized adipocytes (Applicants note that the 3T3-F442A cells disclosed in Sandouk *et al.* were differentiated into adipocytes before running the glucose uptake assay). In particular, Mueller *et al.* 1998 used rat adipocytes, as disclosed in the specification. The incubation periods of the adipocytes prior to measuring glucose uptake range from 15 minutes as disclosed in Sandouk *et al.*, to 24, 48, 72, or 96 hours as disclosed in Mueller *et al* 2000. Thus the 4 and 16 hour incubations used in the specification are well within the range established as valid within the literature. Applicants note that such details as the incubation with metformin or vanadium as disclosed in Mueller *et al.* 2000 are not relevant, as the purpose of the Mueller experiments was specifically to test the effects of metformin or vanadium on glucose transport.

Applicants note that because most of the experiments described in the cited literature were concerned with stimulation of glucose uptake, they do not describe their data in terms of a stimulatory and inhibitory scale. However, the expression of data as a percentage of the control, instead of in specific numbers, is hardly unusual, and a similar scale is used, for example, in Figs. 1-4 of Sandouk *et al.* Further, the specification clearly discloses that the inhibition of glucose transport by PRO1760 was decreased by at least 50% as compared to the control (see the specification at page 512, line 3-6).

Applicants remind the PTO that, as discussed above, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence. Therefore, the legal standard for patentable utility is not absolute certainty. Applicants submit that clear evidence supports the glucose uptake inhibition activity of PRO1760. The Examiner's statements regarding minor assay protocol variations do not suffice to make it more likely than not that one of skill in the art would doubt the truth of this asserted

utility of PRO1760 as an inhibitor of glucose uptake.

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO1760, that are capable of modulating glucose uptake have a substantial, practical, real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as treatments for glucose uptake related diseases, including obesity and diabetes, are envisioned for PRO1760 and the claimed antibodies that specifically bind it, based on the glucose/FFA uptake assay results disclosed herein.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the PRO1760 polypeptide and for the claimed antibodies which specifically bind to the PRO1760 polypeptide. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2830 P1C41**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

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